(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 April 2004 (29.04.2004)

PCT

(10) International Publication Number
WO 2004/035544 A1

(51) International Patent Classification[7]: C07D 223/16, 405/06, 409/06, 403/12, 401/12, A61K 31/55, A61P 25/00

(21) International Application Number: PCT/EP2003/011421

(22) International Filing Date: 14 October 2003 (14.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0224083.6 16 October 2002 (16.10.2002) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

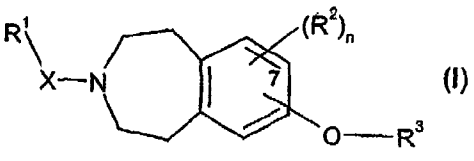
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/035544 A1

(54) Title: BENZO[D]AZEPINE DERIVATIVES FOR THE TREATMENT OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS



(I)

(57) Abstract: The present invention relates to novel benzazepine derivatives of formula (I) having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

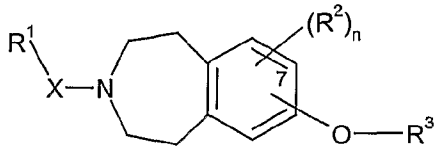
BENZO'D!AZEPINE DERIVATIVES FOR THE TREATMENT OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS

The present invention relates to novel benzazepine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

WO 02/76925 (Eli Lilly) describes a series of compounds which are claimed to be histamine H3 antagonists. WO 01/87834 (Takeda) describes a series of bicyclic heterocycles which are claimed to be melanin-concentrating hormone antagonists.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists and/or inverse agonists such as the current series could be useful for the treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I):



(I)

wherein:

R^1 represents hydrogen, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl,- heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -heterocyclyl-heterocyclyl,

wherein R^1 may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl, pentafluoroethyl, C_{1-6} alkoxy, C_{2-6} alkenyl, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $NR^{15}R^{16}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}R^{16}SO_2$ or $SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

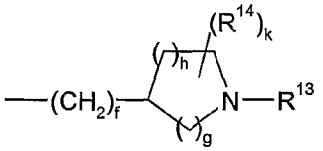
X represents bond, C_{1-6} alkyl, CO, SO_2 or $CONR^4$, such that when R^1 represents -C_{3-8} cycloalkyl, X represents C_{1-6} alkyl, CO, SO_2 or $CONR^4$;

R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

n is 0, 1 or 2;

R^4 represents hydrogen or C_{1-6} alkyl, or together with R^1 may form a heterocyclyl group;

R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;

R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent an N-linked nitrogen containing heterocyclic group optionally substituted by one or more R^{17} groups;

R^{13} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl or heterocyclyl;

R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH, diC_{1-6} alkylamino, C_{1-6} alkoxy or heterocyclyl;

f and k independently represent 0, 1 or 2;

g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;

or a pharmaceutically acceptable salt thereof.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered saturated or partially unsaturated aliphatic ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, diazepanyl, azepanyl, azocanyl and dioxolanyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, benzodioxolyl and dihydroisoquinolinyl.

The term "nitrogen containing heterocyclyl" is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, R^1 represents hydrogen, C_{1-6} alkyl (eg. methyl, i-propyl, t-butyl), C_{3-8} cycloalkyl (eg. cyclopropyl or cyclohexyl), aryl, heteroaryl (eg. thienyl) or heterocyclyl (eg. benzodioxolyl or tetrahydrofuranyl), optionally substituted by one or more C_{1-6} alkoxy groups (eg. methoxy). More preferably, R^1 represents C_{1-6} alkyl (eg. methyl, i-propyl, t-butyl) or C_{3-8} cycloalkyl (eg. cyclopropyl or cyclohexyl).
Preferably, X represents a bond, C_{1-6} alkyl (eg. CH_2) or CO, more preferably bond or C_{1-6} alkyl (eg. CH_2).

More preferably, R^1-X- represents

hydrogen-;

C_{1-6} alkyl- (eg. methyl, i-butyl-, propyl- or ethyl-) optionally substituted by one or more halogen (eg. fluorine), cyano, C_{1-6} alkoxy groups (eg. methoxy), $CONR^{15}R^{16}$ (eg. $-CON(ethyl)_2$) or arylsulfonyl (eg. $-SO_2$-phenyl) groups;

C_{3-8} cycloalkyl-CH_2- (eg. cyclopropyl-CH_2- or cyclohexyl-CH_2-);

aryl- (eg. phenyl) optionally substituted by one or more halogen (eg. chlorine) or C_{2-6} alkenyl (eg. propenyl) groups;

aryl-CH_2- (eg. phenyl-CH_2- or naphthyl-CH_2-) optionally substituted by one or more halogen (eg. chlorine), cyano, $NR^{15}R^{16}$ (eg. $-N(Me)_2$), $NR^{15}COR^{16}$ (eg. NHCOMe) or C_{1-6} alkoxy groups (eg. methoxy);

heterocyclyl-CH_2- (eg. tetrahydrofuranyl-CH_2- or dioxolanyl-CH_2-);

C_{1-6} alkyl-CO- (eg. methyl-CO- or t-butyl-CO-);
aryl-CO- (eg. phenyl-CO- or naphthyl-CO-) optionally substituted by one or more halogen (eg. chlorine) or C_{1-6} alkoxy groups (eg. methoxy);
heteroaryl-CO- (eg. thienyl-CO- or benzofuranyl-CO-);
heterocyclyl-CO- (eg. benzodioxolyl-CO-);
C_{1-6} alkyl-NR^4CO- (eg. isopropyl-NH-CO-);
aryl-NR^4CO- (eg. phenyl-NH-CO-) optionally substituted by one or more halogen (eg. chlorine) atoms;
C_{1-6} alkyl-SO_2- (eg. butyl-SO_2-); or
aryl-SO_2- (eg. phenyl-SO_2-) optionally substituted by one or more halogen (eg. chlorine) atoms.

Yet more preferably, R^1-X- represents
hydrogen-;
C_{1-6} alkyl- (eg. methyl, i-butyl- or ethyl-) optionally substituted by one or more halogen (eg. fluorine), cyano, C_{1-6} alkoxy groups (eg. methoxy), $CONR^{15}R^{16}$ (eg. –CON(ethyl)$_2$) or arylsulfonyl (eg. –SO_2-phenyl) groups;
C_{3-8} cycloalkyl-CH_2- (eg. cyclopropyl-CH_2- or cyclohexyl-CH_2-);
aryl- (eg. phenyl) optionally substituted by one or more C_{2-6} alkenyl (eg. propenyl) groups;
aryl-CH_2- (eg. phenyl-CH_2- or naphthyl-CH_2-) optionally substituted by one or more halogen (eg. chlorine), cyano, $NR^{15}R^{16}$ (eg. –N(Me)$_2$), $NR^{15}COR^{16}$ (eg. NHCOMe) or C_{1-6} alkoxy groups (eg. methoxy); or
heterocyclyl-CH_2- (eg. tetrahydrofuranyl-CH_2-).

Preferably, n represents 0 or 1, more preferably 0.
When n represents 1, R^2 is preferably an amino group.
Preferably, R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$.
Preferably, q represents 2 or 3, more preferably 3.
Preferably, R^{11} and R^{12} independently represent C_{1-6} alkyl (eg. methyl or ethyl).
Alternatively and preferably, $NR^{11}R^{12}$ represents piperidinyl, pyrrolidinyl, morpholinyl, azepanyl or diazepanyl optionally substituted by one or more C_{1-6} alkyl (eg. methyl) or heterocyclic groups (eg. piperidine).
More preferably, $NR^{11}R^{12}$ represents unsubstituted piperidinyl, pyrrolidinyl or azepanyl.
When R^3 represents a group of formula (i), preferably f represents 0 or 1, h represents 1, g represents 2, k represents 0 and R^{13} represents C_{1-6} alkyl (eg. isopropyl). When R^3 represents a group of formula (i), more preferably f represents 0, h represents 1, g represents 2, k represents 0 and R^{13} represents C_{1-6} alkyl (eg. isopropyl).
Preferably, -O-R^3 is present at the 7-position of the benzazepine group.

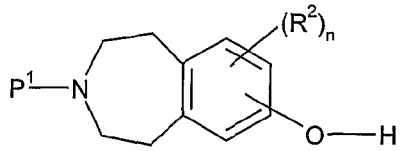
Preferred compounds according to the invention include examples E1-E54 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of compounds of formula (I) therefore form an aspect of the invention.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

wherein R^2 and n are as defined above and P^1 represents R^1-X or a suitable protecting group such as t-butoxycarbonyl, wherein R^1 and X are as defined above, with a compound of formula $R^{3'}$-L^1, wherein $R^{3'}$ is as defined above for R^3 or a group convertible thereto and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine or chlorine) or an optionally activated hydroxyl group, followed as necessary by deprotection under acidic conditions and conversion of $R^{3'}$ to R^3; or

(b) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(c) interconversion to other compounds of formula (I).

When R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$, process (a) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of a transfer reagent such as potassium iodide at an appropriate temperature such as reflux.

When a group $R^{3'}$ convertible to R^3 represents, for example, L^2-$(CH_2)_q$-, process (a) typically comprises an alkylation reaction using analogous conditions to those described above.

When R^3 represents a group of formula (i) and L^1 represents an optionally activated hydroxyl group, process (a) typically comprises the use of a phosphine such as triphenylphosphine in a suitable solvent such as tetrahydrofuran, followed by addition of an azadicarboxylate such as diethylazaodicarboxylate at a suitable temperature such as room temperature.

In process (b), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (c) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, compounds of formula (I) wherein X is other than a bond and R^1 is other than hydrogen may be prepared by the above interconversion procedures.

More specifically, compounds of formula (I) wherein –X-R^1 represents C_{1-6} alkyl may be prepared by interconverting a compound of formula (I) wherein –X-R^1 represents hydrogen in the presence of an appropriate carboxaldehyde or ketone. Such interconversion may occur in the presence of a suitable reducing agent such as a borohydride in the presence of a suitable solvent. Reaction with an appropriate carboxaldehyde may also be performed in the presence of sodium triacetoxyborohydride in the presence of a suitable solvent such as dichloromethane at a suitable temperature (eg. room temperature).

Compounds of formula (I) wherein –X-R^1 represents C_{1-6} alkyl may also be prepared by interconverting a compound of formula (I) wherein –X-R^1 represents hydrogen in the presence of an appropriate C_{1-6} alkyl group containing a suitable leaving group (such as chlorine, bromine, iodine, methanesulfonyloxy and trifluoromethanesulfonyloxy). Such interconversion may occur in the presence of a suitable base (such as potassium carbonate) and a suitable solvent (such as butan-2-one) optionally in presence of heat.

Compounds of formula (I) wherein X represents CO may be prepared by interconverting a compound of formula (I) wherein –X-R^1 represents hydrogen in the presence of an acid halide. Such interconversion may occur in the presence of a suitable base (such as

triethylamine) and a suitable solvent (such as dichloromethane) at a suitable temperature (such as room temperature).

Compounds of formula (I) wherein X represents CO may also be prepared by interconverting a compound of formula (I) wherein $-X-R^1$ represents hydrogen in the presence of an appropriate carboxylic acid. Such interconversion may occur in the presence of a suitable coupling reagent (such as dicyclohexylcarbodiimide) in the presence of a suitable solvent (such as dichloromethane) at a suitable temperature (such as room temperature).

Compounds of formula (I) wherein X represents SO_2 may be prepared by interconverting a compound of formula (I) wherein $-X-R^1$ represents hydrogen in the presence of a sulfonyl chloride. Such interconversion may occur in the presence of a suitable solvent (such as 2-butanone).

Compounds of formula (I) wherein X represents $CONR^4$ may be prepared by interconverting a compound of formula (I) wherein $-X-R^1$ represents hydrogen in the presence of a compound of formula R^1-N=C=O, wherein R^1 is as defined above. Such interconversion may occur in the presence of a suitable solvent (such as 2-butanone).

Compounds of formula (I) wherein X represents $CONR^4$ may also be interconverted by reacting a compound of formula (I) wherein $-X-R^1$ represents hydrogen sequentially with phosgene in a solvent such as toluene followed by a compound of formula R^4R^1-NH, in a solvent such as dichloromethane and a suitable base, such as triethylamine, wherein R^1 and R^4 are as defined above.

Compounds of formula (II) may be prepared in an analogous manner to those described in Description 3 of WO 02/40471.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive dysfunction, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia, attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1
7-(3-Chloro-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D1)

7-Hydroxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (Description 3 in PCT publication number WO 02/40471) (13.15g, 50mmol) and potassium carbonate (20.7g, 150mmol) were suspended in 2-butanone (75ml). 1-Bromo-3-chloropropane (7.4ml, 75mmol) was added dropwise to the mixture and heated at reflux for 48 hours. The solids were filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (1:5) to afford the title compound (D1) (15.36g, 91%). ^{1}H NMR ($CDCl_3$) 7.03 (1H, d, J 8.1Hz), 6.62 (2H, m), 4.08 (2H, m), 3.73 (2H, m), 3.54 (4H, m), 2.84 (4H, m), 2.22 (2H, m), 1.48 (9H, s).

Description 2
7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D2)

7-(3-Chloro-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D1) (6.80g, 20 mmol) and potassium carbonate (8.34g, 60mmol) were suspended in 2-butanone (50 ml). Piperidine (3.96ml, 40mmol) was added and the mixture heated at reflux for 24 hours. The solids were filtered and the filtrate concentrated *in vacuo*. The residue purified by column chromatography, eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (1:9:90) to afford the title compound (D2) (6.45g, 83%). MS (ES+) m/e 390 $[M+H]^+$.

Description 3

7-(2-Piperidin-1-yl-ethoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D3)

A mixture of 7-hydroxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid tert-butyl ester (Description 3 in PCT publication number WO 02/40471) (2.63g, 10mmol), 1-(2-chloroethyl)piperidine hydrochloride (3.68g, 20mmol) and potassium carbonate (4.14g, 30mmol) in N,N-dimethyl formamide (30ml) was heated at 80°C for 24 hours. After cooling the mixture was diluted with water and ethyl acetate. The organic phase was separated washed with water, brine, dried and evaporated *in vacuo*. The residue was purified by column chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (1:9:90) to afford the title compound (D3) (643mg, 17%); MS (ES+), m/e 375 $[M+H]^+$.

Description 4

1,1-Dimethylethyl 7-({1-[(2-propen-1-yloxy)carbonyl]-4-piperidinyl}oxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D4)

2-Propen-1-yl 4-hydroxy-1-piperidinecarboxylate (J.Med. Chem.,1998, **41(25)**, 4983-4994) (6.64g, 36 mmol), and triphenylphosphine (9.39g, 36 mmol) were dissolved in tetrahydrofuran (100 ml) at 0°C. 7-Hydroxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (Description 3 in PCT publication number WO 02/40471) (7.55g, 29 mmol) was added followed by dropwise addition of diethyl azodicarboxylate (5.65 ml, 36 mmol) and the solution stirred at room temperature for 72 hours. The reaction was concentrated *in vacuo* and the residue partitioned between 1M sodium hydroxide solution and ethyl acetate. The organic layer was washed successively with 1M sodium hydroxide solution, water, brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to a crude oil which was purified by column chromatography, eluting with a mixture hexane:ethylacetate (1:10) then ethylacetate to afford the title compound (7.01g, 56%) MS (ES+) m/e 431 $[M+H]^+$.

Description 5

1,1-Dimethylethyl 7-(4-piperidinyloxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D5)

1,1-Dimethylethyl 7-({1-[(2-propen-1-yloxy)carbonyl]-4-piperidinyl}oxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D4) (4.30g, 10 mmol) and dimedone (14.02

g, 100 mmol) were dissolved in THF (300 ml) at 0°C. Tetrakistriphenyphosphinepalladium(0) (2.30g, 2mmol) was added and the solution stirred at room temperature for 24 hours. Solvents were removed *in vacuo* and the residue was partitioned between 3M sodium hydroxide solution and diethyl ether. The organic phase was washed with 3M soidium hydroxide solution (x3), water (x3), brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to a crude solid. The solid was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (D9) (1.70g, 49%) MS (ES+) m/e 347 $[M+H]^+$.

Description 6

1,1-Dimethylethyl 7-{[1-(1-methylethyl)-4-piperidinyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D6)

1,1-Dimethylethyl 7-(4-piperidinyloxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D5) (346 mg, 1mmol) and acetone (734 μL, 10 mmol) were stirred in a mixture of 5% acetic acid in dichloromethane for 1 hour. The solution was treated with sodium triacetoxyborohydride (2.11g, 10mmol) and the suspension stirred at room temperature for 16 hours. The mixture was partitioned between saturated sodium carbonate and dichloromethane. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to a crude solid. The solid was purified by column chromatography eluting with dichloromethane then a mixture of.880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (211mg, 54%); MS (ES+) m/e 389 $[M+H]^+$.

Description 7

1,1-Dimethylethyl 7-[({1-[(2-propen-1-yloxy)carbonyl]-4-piperidinyl}methyl)oxy]-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D7)

The title compound was prepared in an analogous manner to that used for D4 using 2-propen-1-yl 4-(hydroxymethyl)-1-piperidinecarboxylate (EP 394991) and 7-hydroxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (Description 3 in PCT publication number WO 02/40471) to afford the title compound (3.24g, 73%); MS (ES+) m/e 445 $[M+H]^+$.

Description 8

1,1-Dimethylethyl 7-[(4-piperidinylmethyl)oxy]-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D8)

The title compound was prepared from 1,1-dimethylethyl 7-[({1-[(2-propen-1-yloxy)carbonyl]-4-piperidinyl}methyl)oxy]-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D7) in an analogous manner to that used in D5 to afford the title compound (1.06g, 59%); MS (ES+) m/e 361 $[M+H]^+$.

Description 9

1,1-Dimethylethyl 7-({[1-(1-methylethyl)-4-piperidinyl]methyl}oxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D9)

The title compound was prepared from 1,1-dimethylethyl 7-[(4-piperidinylmethyl)oxy]-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D8) in an analogous manner to that used in D6 to afford the title compound (283 mg, 70%); MS (ES+) m/e 403 $[M+H]^+$.

Description 10

7-Amino-8-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D10)

Step 1: 7-Nitro-8-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester

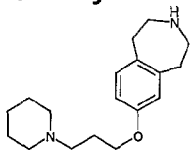
The title compound was prepared from 7-Hydroxy-8-nitro-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (WO 0368752) and 1-(2-chloroethyl)piperidine hydrochloride in an analogous manner to that used in D3 except methyl ethyl ketone was used instead of dimethylformamide; MS (ES+), m/e 434 $[M+H]^+$.

Step 2: 7-Amino-8-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester

The product of Step 1 (1.54g, 3.55mmol) was dissolved in ethanol (50ml), treated with 10% palladium on charcoal and shaken under a pressure of hydrogen (50psi) for 2 hours. The reaction mixture was then filtered and the filtrate reduced in vacuo to furnish the title compound; MS (ES+), m/e 404 $[M+H]^+$.

Example 1

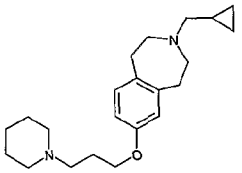
7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E1)



7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D2) (6.18g, 16mmol) was dissolved in dichloromethane (30ml) at 0°C and treated with trifluoroacetic acid (30ml). The solution was stirred at room temperature for one hour and solvents removed *in vacuo*. The residue was partitioned between ethyl acetate and 2N sodium hydroxide solution and the organic layer separated. The aqueous phase was extracted with ethyl acetate (x5). The combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by column chromatography eluting initially with dichloromethane then a mixture of 0.880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (E1) MS (ES+) m/e 289 $[M+H]^+$.

Example 2

3-Cyclopropylmethyl-7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E2)



The crude product of Example 1 (200 mg, 0.7 mmol) and cyclopropanecarboxaldehyde (79 µL, 1.1 mmol) were stirred at room temperature for 2 hours in 5% acetic acid in dichloromethane. The solution was then treated with sodium triacetoxyborohydride (297mg, 1.4mmol) and the suspension stirred at room temperature for 16 hours. The resulting solution was applied directly to a SCX cartridge (Varian bond-elute, 10g) and eluted with methanol then a mixture of .880 ammonia:methanol (1:9). The basic fractions were then reduced *in vacuo* and the residue purified by column chromatography, eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound; (189mg, 79%), MS(ES+) m/e 343 $[M+H]^+$.

Examples 3-11

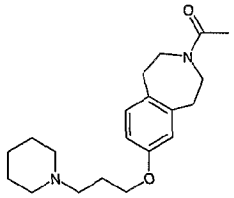
Examples 3-11 (E3-E11) were prepared using an analogous method to that described in Example 2 (E2) by substituting cyclopropanecarboxaldehyde for the appropriate aldehyde indicated in the table.

Example	Aldehyde Intermediate	Mass Spectrum
3-(4-Methoxy-benzyl)-7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E3)	4-Methoxybenzaldehyde	MS(ES+) m/e 409 $[M+H]^+$.
3-Cyclohexylmethyl-7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E4)	Cyclohexane carboxaldehyde	MS(ES+) m/e 385 $[M+H]^+$.
7-(3-Piperidin-1-yl-propoxy)-3-(tetrahydro-furan-2-ylmethyl)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E5)	Tetrahydrofuran-2-carboxaldehyde (50% aqueous solution)	MS(ES+) m/e 373 $[M+H]^+$.
3-(Phenylmethyl)-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E6)	benzaldehyde	MS(ES+) m/e 379 $[M+H]^+$.
3-(2-Naphthalenylmethyl)-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E7)	2-napthaldehyde	MS(ES+) m/e 429 $[M+H]^+$.
3-[(2E)-3-Phenyl-2-propen-1-yl]-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E8)	trans-cinnamaldehyde	MS(ES+) m/e 405 $[M+H]^+$.

4-[(7-{[3-(1-Piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)methyl]benzonitrile (E9)	4-cyanobenzaldehyde	MS(ES+) m/e 404 $[M+H]^+$.
N,N-Dimethyl-4-[(7-{[3-(1-piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)methyl]aniline (E10)	4-dimethylamino benzaldehyde	MS(ES+) m/e 421 $[M+H]^+$.
N-{4-[(7-{[3-(1-Piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)methyl]phenyl}acetamide (E11)	4-acetamido benzaldehyde	MS(ES+) m/e 436 $[M+H]^+$.

Example 12

1-[7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepin-3-yl]-ethanone (E12)



7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E1) (200mg, 0.7mmol) and triethylamine (117μL, 0.84mmol) were dissolved in dichloromethane (3ml). The solution was treated with acetyl chloride (57μL, 0.77mmol) and stirred at room temperature for 16 hours. The solvent was removed *in vacuo,* and the residue purified by column chromatography eluting dichloromethane and then .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (E12) (178 mg, 63%), MS(ES+) m/e 331 $[M+H]^+$.

Examples 13-17

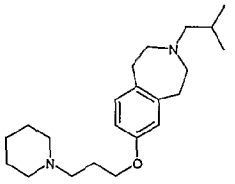
Examples 13-17 (E13-E17) were prepared using an analogous method to that described in Example 12 (E12) by substituting acetyl chloride for the appropriate acid chloride indicated in the table.

Example	**Acid chloride Intermediate**	**Mass Spectrum**
1-Naphthalen-1-yl-1-[7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepin-3-yl]-methanone (E13)	1-Naphthoyl chloride	MS(ES+) m/e 443 $[M+H]^+$.
2,2,-Dimethyl-1-[7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepin-3-yl]-propan-1-one (E14)	Trimethylacetyl chloride	MS(ES+) m/e 373 $[M+H]^+$.
1-(4-Methoxy-phenyl)-1-[7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-	4-Methoxybenzoyl chloride	MS(ES+) m/e 423 $[M+H]^+$.

benzo[*d*]azepin-3-yl]-methanone (E15)		
1-[7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepin-3-yl]-1-thiophen-2-yl-methanone (E16)	Thiophene-2-carboxylic acid chloride	MS(ES+) m/e 399 $[M+H]^+$.
1-Benzo[1,3]dioxol-5-yl-1-[7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepin-3-yl]-methanone (E17)	Piperonyloyl chloride	MS(ES+) m/e 437 $[M+H]^+$.

Example 18

3-Isobutyl-7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E18)



7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E1) (361mg, 1mmol) and potassium carbonate (417mg, 3 mmol) was suspended in 2-butanone (20 ml). The mixture was treated with isobutyliodide (127μL, 1.1mmol) and heated at reflux for 16 hours. The solids were filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography eluting with a mixture of 0.880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (E18) (184mg, 53%), MS(ES+) m/e 345 $[M+H]^+$.

Examples 19-26

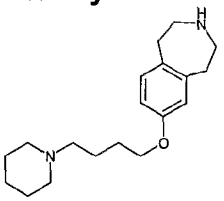
Examples 19-26 (E19-E26) were prepared from Description 1 (D1) in a two step procedure using an analogous method to that described in Description 2 (D2) followed by an analogous method described in Example 1 (E1) by substituting piperidine for the appropriate amine indicated in the table.

Example	**Amine Intermediate**	**Mass Spectrum**
7-(3-Azepan-1-ylpropoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E19)	Azepane	MS(ES+) m/e 303 $[M+H]^+$.
7-(3-[1,4]-Diazepan-1-ylpropoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E20)	[1,4]-Diazepane-1-carboxylic acid *tert*-butyl ester	MS(ES+) m/e 304 $[M+H]^+$.
Diethyl-[3-(2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)propyl]amine (E21)	Diethylamine	MS(ES+) m/e 277 $[M+H]^+$.
7-[3-(2,5-Dimethylpyrrolidin-1-yl)propoxy]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E22)	2,5-Dimethylpyrrolidine	MS(ES+) m/e 303 $[M+H]^+$.
7-(3-[1,4']-Dipiperidinyl-1'-yl propoxy)-2,3,4,5-	[1,4']-Bipiperidinyl	MS(ES+) m/e

tetrahydro-1*H*-benzo[*d*]azepine (E23)		372 $[M+H]^+$.
7-(3-Morpholin-4-ylpropoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E24)	Morpholine	MS(ES+) m/e 291 $[M+H]^+$.
Dimethyl-[3-(2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)propyl]amine (E25)	Dimethylamine	MS(ES+) m/e 249 $[M+H]^+$.
7-(3-Pyrrolidin-1-ylpropoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E26)	Pyrrolidine	MS(ES+) m/e 275 $[M+H]^+$.

Example 27

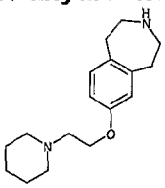
7-(4-Piperidin-1-yl-butoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E27)



The title compound (E27) was prepared from 7-hydroxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid tert-butyl ester (Description 3 in WO 02/40471) and 1,4-dibromobutane using an analogous method to that described in Description 1 (D1) followed by Description 2 (D2) and Example 1 (E1) MS(ES+) m/e 303 $[M+H]^+$.

Example 28

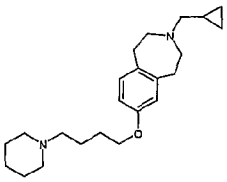
7-(2-Piperidin-1-yl-ethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E28)



The title compound (E28) was prepared from 7-(2-piperidin-1-yl-ethoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D3) using the method described in Example 1 (E1) MS(ES+) m/e 274 $[M+H]^+$.

Example 29

3-Cyclopropylmethyl-7-(4-piperidin-1-yl-butoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E29)

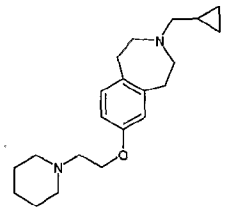


A mixture of 7-(4-piperidin-1-yl-butoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E27) (150mg, 0.5mmol), cyclopropanecarboxaldehyde (53mg, 0.75mmol), acetic acid (0.1ml)

and (polystyrylmethyl)trimethylammonium cyanoborohydride (250mg, 4mmol/g loading, 1mmol) in methanol (5ml) was stirred at room temperature for 18 hours. The reaction mixture was applied to an SCX column (Varian bond-elute, 10g) eluting with methanol followed by a mixture of 0.880 ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* giving the title compound (E29) MS(ES+) m/e 357 $[M+H]^+$.

Example 30

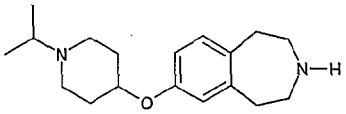
3-Cyclopropylmethyl-7-(2-piperidin-1-yl-ethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E30)



The title compound (E30) was prepared from 7-(2-piperidin-1-yl-ethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E28) using an analogous method to that described in Example 29 (E29). MS(ES+) m/e 329 $[M+H]^+$.

Example 31

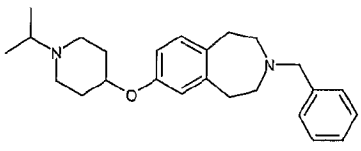
7-{[1-(1-Methylethyl)-4-piperidinyl]oxy}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E31)



1,1-Dimethylethyl 7-{[1-(1-methylethyl)-4-piperidinyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D6) (200 mg, 0.69 mmol) was stirred at room temperature in a 1:1 solution of dichloromethane:trifluoroacetic acid (10ml) for 1 hour. The solution was concentrated *in vacuo* and the residue co-evaporated with dichloromethane three times. The residue was passed through a SCX cartridge (Varian, 10g), washing with methanol and eluting products with 10% .880 ammonia in methanol. The ammonia solution was concentrated *in vacuo* and the residue purified by column chromatography, eluting with a dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:190), to afford the title compound (160mg, 65%); MS (ES+) m/e 289 $[M+H]^+$.

Example 32

7-{[1-(1-Methylethyl)-4-piperidinyl]oxy}-3-(phenylmethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E32)



The title compound was prepared from 7-{[1-(1-methylethyl)-4-piperidinyl]oxy}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E31) and benzaldyhyde using the general method described in Example 29 to afford the title compound (7.01g, 56%); MS (ES+) m/e 431 $[M+H]^+$.

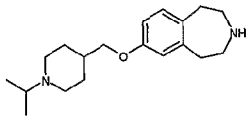
Examples 33-34

The following examples were prepared according to the general method in Example 32, substituting benzaldehyde with the appropriate Aldehyde.

Example	Aldehyde	Mass Spectrum
3-[(3,4-Dichlorophenyl)methyl]-7-{[1-(1-methylethyl)-4-piperidinyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E33)	3,4-dichloro benzaldehyde	MS(ES+) m/e 447 448 449 450$[M+H]^+$.
3-Cyclopropylmethyl-7-(1-isopropyl-piperidin-4-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E34)	Cyclopropane carboxaldehyde	MS(ES+) m/e 343 $[M+H]^+$.

Example 35

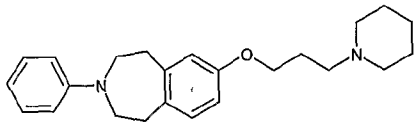
7-({[1-(1-Methylethyl)-4-piperidinyl]methyl}oxy)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E35)



The title compound was prepared from 1,1-dimethylethyl 7-({[1-(1-methylethyl)-4-piperidinyl]methyl}oxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D9) in an analogous manner to that used in E31 to afford the title compound (E35) (178 mg, 80%); MS (ES+) m/e 303 $[M+H]^+$.

Example 36

3-Phenyl-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E36)



7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E1) (216mg, 0.75 mmol), iodobenzene (100 µL, 0.9 mmol), *rac*-2,2-bis(diphenylphosphino)-1,1-binapthyl (35 mg, 0.06 mmol) and sodium *tert*-butoxide (80 mg, 0.83 mmol) were suspended in toluene (10 ml) and treated with tris(dibenzylideneacetone) dipalladium(0) (35 mg, 0.04 mmol). The mixture was then heated at reflux for 24 hours, cooled, and then applied directly to a SCX ion exchange cartridge (Varian, 10g), eluting with methanol and then a mixture of .880 ammonia:methanol (1:9). The ammonia fractions were concentrated *in vacuo* and the residue purified by column chromatography, eluting with dichloromethane

then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (90mg, 33%); MS (ES+) m/e 365 $[M+H]^+$.

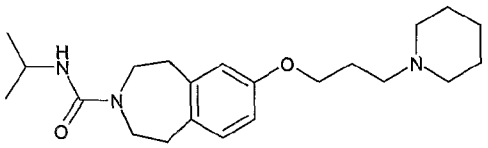
Examples 37-38

The following examples were prepared according to the general method in E36, substituting iodobenzene with the appropriate aryl halide.

Example	Aryl Halide	Mass Spectrum
4-(7-{[3-(1-Piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)benzonitrile (E37)	4-bromobenzonitrile	MS(ES+) m/e390 $[M+H]^+$.
3-(3,4-Dichlorophenyl)-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E38)	1-bromo-3,4-dichlorobenzene	MS(ES+) m/e 434 435 436 437 $[M+H]^+$.

Example 39

***N*-(1-Methylethyl)-7-{[3-(1-piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxamide (E39)**



The dihydrochloride salt of 7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E1) (361 mg, 1 mmol), and triethylamine (418 µl, 3 mmol), were dissolved in dichloromethane (5 ml). The solution was treated with isopropyl isocyanate (102 mg, 1.2 mmol) and stirred at room temperature for 16 hours. The solution was concentrated *in vacuo* to a crude solid that was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90), to afford the title compound (270mg, 74%); MS (ES+) m/e 374 $[M+H]^+$.

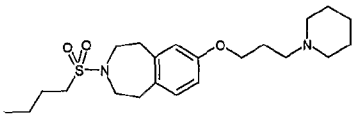
Examples 40-41

The following examples were prepared according to the general method described for E39 substituting phenyl isocyanate for the appropriate isocyanate.

Example	Isocyanate	Mass Spectrum
N-Phenyl-7-{[3-(1-piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxamide (E40)	phenylisocyanate	MS(ES+) m/e 408 $[M+H]^+$.
N-(3,4-Dichlorophenyl)-7-{[3-(1-piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxamide (E41)	3,4-dichlorophenyl isocyanate	MS(ES+) m/e 498, 499, 500, 501 $[M+H]^+$.

Example 42

3-(Butylsulfonyl)-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E42)



The dihydrochloride salt of 7-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E1) (361 mg, 1 mmol), and triethylamine (418 µl, 3 mmol), were dissolved in dichloromethane (5 ml). The solution was treated with 1-butane sulfonyl chloride (188 mg, 1.2 mmol) and stirred at room temperature for 16 hours. The solution was concentrated *in vacuo* to a crude solid that was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90), to afford the title compound (176mg, 43%); MS (ES+) m/e 374 $[M+H]^+$.

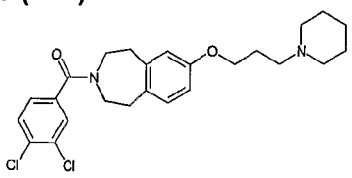
Examples 43-44

The following examples were prepared according to the general method general method described for E42 substituting 1-butane sulfonyl chloride for the appropriate sulphonyl chloride.

Example	Sulphonyl Chloride	Mass Spectrum
3-(Phenylsulfonyl)-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E43)	benzenesulfonyl chloride	MS(ES+) m/e 429 $[M+H]^+$.
3-[(3,4-Dichlorophenyl)sulfonyl]-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E44)	3,4-dichlorobenzenesulfonyl chloride	MS(ES+) m/e 497, 498, 499, 500 $[M+H]^+$.

Example 45

3-[(3,4-Dichlorophenyl)carbonyl]-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E45)



3,4-Dichlorobenzoic acid (172 mg, 0.9mmol), N-hydroxybenzotriazole (120 mg, 0.9 mmol) and N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.8 mmol/g) (833 mg, 1.5 mmol) were stirred at room temperature in dichloromethane (5ml). After 15 minutes the product of Example 1 (E1) (216 mg, 0.75 mmol) was added and the slurry stirred for a further 16 hours. The mixture was then applied directly to a SCX ion exchange cartridge (Varian, 10g), eluting with methanol and then a mixture of .880 ammonia:methanol (1:9). The ammonia fractions were concentrated *in vacuo* and the residue purified by column

chromatography, eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90), to afford the title compound (240mg, 69%); MS (ES+) m/e 461/462/463/464 $[M+H]^+$.

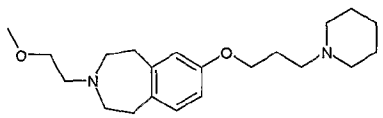
Examples 46-47

The following examples were prepared according to the general method described for E45 substituting 3,4-dichlorobenzoic acid for the appropriate carboxylic acid.

Example	Carboxylic Acid	Mass Spectrum
3-(Phenylcarbonyl)-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E46)	benzoic acid	MS(ES+) m/e 393 $[M+H]^+$.
3-(1-Benzofuran-2-ylcarbonyl)-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E47)	benzofuran-2-carboxylic acid	MS(ES+) m/e 433 $[M+H]^+$.

Example 48

3-[2-(Methyloxy)ethyl]-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E48)



7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E1) (216 mg, 0.75 mmol), 2-bromoethyl methyl ether (78μl, 0.83mmol) and potassium carbonate (311 mg, 2.25 mmol) were suspended in 2-butanone (10 ml) and heated at reflux for 24 hours. The solids were filtered, washed with acetone and concentrated *in vacuo* to a crude oil. The oil was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (205mg, 59%); MS (ES+) m/e 347 $[M+H]^+$.

Examples 49-52

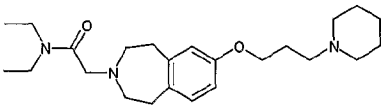
The following examples were prepared according to the general method described for E50 substituting 2-bromoethyl methyl ether for the appropriate alkyl halide.

Example	Alkyl Halide	Mass Spectrum
3-(1,3-Dioxolan-2-ylmethyl)-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E49)	2-bromomethyl-1,3-dioxlane	MS(ES+) m/e 37[illegible] $[M+H]^+$.
3-[2-(Phenylsulfonyl)ethyl]-7-{[3-(1-piperidinyl)propyl]oxy}-2,3,4,5-tetrahydro-1H-3-benzazepine (E50)	2-bromoethyl phenyl sulfone (U.S.5,802,887)	MS(ES+) m/e 45[illegible] $[M+H]^+$.
(7-{[3-(1-Piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3H-3-	bromoacetonitril	MS(ES+) m/e 32[illegible]

benzazepin-3-yl)acetonitrile (E51)	e	$[M+H]^+$.
7-{[3-(1-Piperidinyl)propyl]oxy}-3-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (E52)	1-iodo-3,3,3-trifluoropropane	MS(ES+) m/e 385 $[M+H]^+$.

Example 53

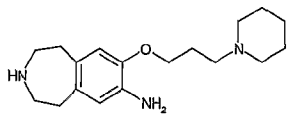
N,N-diethyl-2-(7-{[3-(1-piperidinyl)propyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)acetamide (E53)



7-(3-Piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E1) (361 mg, 1 mmol) and triethylamine (432 μL, 3.1 mmol) were dissolved in methanol (2ml) and treated with chloroacetic acid diethylamine (150 μL, 1 mmol) in acetone (8ml). The solution was stirred at room temperature for 16 hours and concentrated *in vacuo*. The residue was applied to a SCX ion exchange cartridge (Varian, 10g), eluting with methanol and then a mixture of .880 ammonia:methanol (1:9). The ammonia fractions were concentrated *in vacuo* and the residue purified by column chromatography, eluting with a with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (353 mg, 88%); MS (ES+) m/e 402 $[M+H]^+$.

Example 54

8-(3-Piperidin-1-yl-propoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ylamine (E54)



A solution of 7-amino-8-(3-piperidin-1-yl-propoxy)-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D10) (0,1g, 0.25mmol) in methanol (5ml) was treated with a 4M solution of HCl in dioxan (5ml) and stirred at room temperature for 2 hours. The reaction was then reduced in vacuo to to afford the title compound (0.085g); MS (ES+) m/e 304 $[M+H]^+$.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene (Huvar, A. *et al.* (1999) Mol. Pharmacol. **55(6)**, 1101-1107) was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α E. coli host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the sh ble gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10μl of test compound (or 10μl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10μl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/μl or 50μCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80μl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80μl which contains 7.5μg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller. The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10μl of test compound (or 10μl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60μl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60μl which contains 10μg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10μM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10μl histamine (Tocris) at a final concentration of 0.3μM; and

(d) 20μl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/μl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

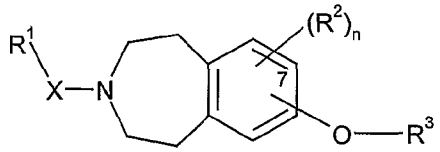
Results

The compounds of Examples E1-54 were tested in the histamine H3 functional antagonist assay and exhibited antagonism in the following range: 6.0.-10.0 pK_b. More particularly, the compounds of Examples E1-11, E13-19, E26, E29-34, E37, E40, E42-44 and E46-54 exhibited antagonism in the following range: 8.0-10.0 pK_b.

Yet more particularly, the compounds of Examples E2-11, E18-19, E26, E29-34, E48 and E50-53 exhibited antagonism in the following range: 8.5-10.0 pK_b.

CLAIMS:

1. A compound of formula (I):



(I)

wherein:

R^1 represents hydrogen, -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl,- heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -heterocyclyl-heterocyclyl,
wherein R^1 may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl, pentafluoroethyl, C_{1-6} alkoxy, C_{2-6} alkenyl, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $NR^{15}R^{16}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}R^{16}SO_2$ or $SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

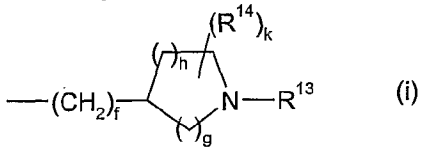
X represents bond, C_{1-6} alkyl, CO, SO_2 or $CONR^4$, such that when R^1 represents -C_{3-8} cycloalkyl, X represents C_{1-6} alkyl, CO, SO_2 or $CONR^4$;

R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

n is 0, 1 or 2;

R^4 represents hydrogen or C_{1-6} alkyl, or together with R^1 may form a heterocyclyl group;

R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;

R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent an N-linked nitrogen containing heterocyclic group optionally substituted by one or more R^{17} groups;

R^{13} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl or heterocyclyl;

R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH, diC_{1-6} alkylamino, C_{1-6} alkoxy or heterocyclyl;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is a compound of formula E1-E54 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition which comprises the compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

4. A compound as defined in claim 1 or claim 2 for use in therapy.

5. A compound as defined in claim 1 or claim 2 for use in the treatment of neurological diseases.

6. Use of a compound as defined in claim 1 or claim 2 in the manufacture of a medicament for the treatment of neurological diseases.

7. A method of treatment of neurological diseases which comprises administering to a host in need thereof an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition for use in the treatment of neurological diseases which comprises the compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11421

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D223/16 C07D405/06 C07D409/06 C07D403/12 C07D401/12
A61K31/55 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 03015 A (SMITHKLINE BEECHAM CORP) 18 February 1993 (1993-02-18) examples 1,2,8,9,11 table I page 11, line 13-15 ---	1,6
X	EP 1 122 252 A (TAKEDA CHEMICAL INDUSTRIES LTD) 8 August 2001 (2001-08-08) reference examples 10 and 18 example 6 page 54, line 16-20 ---	1,6
Y	WO 02 076925 A (BEAVERS LISA SELSAM ;SCHAUS JOHN MEHNERT (US); WATSON BRIAN MORGAN) 3 October 2002 (2002-10-03) cited in the application example 245 claims 13-26 ---	1,6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2004	18/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seitner, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 02 12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) example 86 claims 49-60	1,6
Y	GILLIGAN ET AL: "Novel Piperidine sigma Receptor Ligands as Potential Antipsychotc Drugs" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 23, 1992, pages 4344-4361, XP002106858 ISSN: 0022-2623 abstract; example 18AD; table II	1,6
Y	WO 02 40471 A (STEMP GEOFFREY ;HADLEY MICHAEL STEWART (GB); LIGHTFOOT ANDREW P (G) 23 May 2002 (2002-05-23) example 173 page 22, line 25 -page 24, line 5 claim 1	1,6
Y	WO 00 21951 A (JOHNSON CHRISTOPHER NORBERT ;VONG ANTONIO KUOK KEONG (GB); STEMP G) 20 April 2000 (2000-04-20) example 23 page 16, line 25 -page 17, line 25 claim 1	1,6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/11421

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/11421

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